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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,124	04/28/2000	Ralph A. Nixon	50122/002003	3388

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/560,124	NIXON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *14 October 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet.*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *21 and 26*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *16,17,19,20,22,24,25,27,28 and 30*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Anne-Marie Falk

Anne-Marie Falk, Ph.D.
Primary Examiner
Art Unit: 1632

Continuation Sheet (PTO-303)

Continuation of 3. Applicant's reply has overcome the following rejection(s):

the 35 U.S.C. 112, second paragraph rejection of Claims 16-31.

Continuation of 5. The affidavit and request for reconsideration has been considered but does NOT place the application in condition for allowance because:

The Declaration of Dr. Nixon, filed October 14, 2003, points out that rab5 overexpressing cells *in vitro* and *in vivo* mimic the increased endocytic pathway that is observed in patients with early stage Alzheimer's disease. The Examiner accepts the Declarant's statement that "cells having enlarged endosomes also exhibit increased endocytic pathway activity, which is characterized by specific endosomal changes (e.g., increased endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of Aβ in early endosomes)" (paragraph 8). However, since the *in vivo* experiments described in the Declaration of January 8, 2003 were carried out using HSV to produce mice that acutely overexpress rab5 in mouse brains rather than involving the production of transgenic mice as described in the specification, the phenotype disclosed in the Declaration would not be considered predictive of the phenotype exhibited by rab5 transgenic mice. Furthermore, the claims recite "providing a mouse expressing a transgene comprising a recombinant rab5 nucleic acid that increases activity of the endocytic pathway" and therefore read on mice acutely overexpressing rab5 as described in the Declaration of 1/8/03. However, the specification does not describe acute overexpression of rab5 (somatic cell genetic modification), but rather only discusses transgenic mice overexpressing rab 5. Thus, the skilled artisan would not have had the benefit of the teachings disclosed in the Declaration but not described in the specification. Furthermore, the Declaration filed 1/8/03 states that given their results with HSV infected mice "one skilled in the art would predict that rab5 transgene expression, driven by appropriate promoters, will enlarge endosomes in rab5

overexpressing transgenic mice." Unfortunately, the specification does not provide specific guidance with regard to the type of promoter that should be used in the rab5 transgene construct. Thus, the specification does not provide adequate guidance with regard to the transgenic mice having the specific phenotype recited in the claims.

At pages 9-12 of the response, Applicants argue that the *in vivo* methods of compound screening are enabled by the specification because one of skill in the art would be able to measure endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of Aβ in early endosomes of rab5 transgenic mice. The Examiner accepts that one of skill in the art would be able to measure these various parameters. However, the enablement rejection hinges on the issue of unpredictability of phenotype in transgenic mice.

Thus, the rejection is maintained for reasons of record.